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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Schoenfeld *et al.*		
SERIAL NUMBER:	09/806,400	EXAMINER:	Ronald Schwadron
FILING DATE:	March 30, 2001	ART UNIT:	1644
FOR:	COMPOSITIONS FOR THE PREVENTION AND/OR TREATMENT OF ATHEROSCLEROSIS		

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DECLARATION OF DROR HARATS UNDER 37 C.F.R. §1.132

I, Dror Harats, of 71 Mendes Street, 53 765 Ramat Gan, Israel, declare and state that:

1. I am a coinventor, together with Yahuda Shoenfeld and Jacob George, in the above-referenced patent application.

2. I received an M.D. degree from the Hebrew University Hadassah Medical School, Jerusalem, Israel. I worked as a post-doctoral fellow at the University of California at San Francisco from 1991-1994.

3. I am presently employed as the head of the "Institute of Lipids and Atherosclerosis" at the Sheba Medical Center in Tel-Hashomer, Israel. I am an Associate Professor of Medicine at the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel. I also serve as the Secretary of the Israeli Society for Research, Prevention and Treatment of Atheroclerosis, and drafted the Guidelines for Prevention of Cardiovascular Diseases in Israel, and am a member in good standing of the European Taskforce for Prevention and Treatment of Atherosclerosis and Cardiovascular Diseases.

4. My research focuses on atherosclerosis. Since the beginning of my career, I have published over 80 scientific articles in highly regarded journals and books, and have presented my achievements at many international scientific conferences.

5. I have reviewed the Final Office Action dated July 22, 2005. I understand that Claims 14, 18-20 and 26 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. I appreciate the Examiner's time discussing my invention at the November 2005 interview. In response to that rejection, as discussed at the interview with the Examiner, the claims have now been amended to recite a method of treating atherosclerosis by oral administration of an enteric coated composition comprising isolated copper-oxidized LDL or isolated human copper-oxidized LDL.

6. The specification provides an example in a mouse model (as described in the Specification at, *e.g.*, page 15, lines 20-29; and page 18, line 18 to page 19, line 31). I believe that the LDLR deficient mice used in the studies disclosed in the present application is the preferred, art-recognized model for atherosclerosis, for the reasons outlined below.

Specifically, mice having targeted inactivation of the apolipoprotein E (ApoE) gene and of the LDLR gene, under appropriate conditions, develop complex atherosclerotic lesions and provide practical atherosclerotic mouse models and are the most utilized model to study lipids and atherosclerosis. ApoE is critical in lipoprotein trafficking (clearance of chylomicrons, VLDL, and HDL). Thus mice lacking apoE have plasma cholesterol levels that are 4 to 5 times normal and develop atherosclerotic lesions spontaneously, even when fed a normal diet. The lesions resemble human lesions and progress over time from an initial fatty streak to a complex lesion with a fibrous cap. Mice lacking the LDLR have less overt disease, with a modest 2 times normal plasma cholesterol level when maintained on a normal diet, and they develop atherosclerosis only slowly. However, in response to a high-fat, high-cholesterol diet, LDLR-deficient mice exhibit massive elevations in plasma cholesterol and rapidly develop atherosclerotic lesions throughout the aorta.

The predictable development of atherosclerotic lesions and plaques and there resemblance to human atherosclerotic lesions and plaques along with other more general advantages of mice, such as their small size, short generation time, and relative ease to care, have made the mouse a most valid, effective and practical model for the study of atherosclerosis.

Although the LDL-receptor deficient mouse isn't the optimal model for genetic human familial hypercholesterolemia, it is one of the most predictable models for human atherosclerosis and the likelihood of new molecules to work as anti-atherosclerosis drugs in humans is high. Human atherosclerotic plaques are infiltrated with lymphocytes and display an inflammatory phenotype that includes expression of pro-inflammatory cytokines. In this sense the LDL-receptor deficient mice have plaques similar to those of humans containing a significant number of lymphocytes. Moreover, therapeutic strategies that apply for atheroprotection in humans are similarly successful in LDL receptor deficient mice and may not be so in ApoE knockout mice. These findings indicate that plaques developing in LDL receptor deficient mice may be more relevant to human atherosclerosis than other non-human models and is one of the most widely employed models for drug development in the field of atherosclerosis.

7. I believe that the present invention provides a range of concentrations of the composition to treat atherosclerosis (*See, e.g.*, page 18, lines 27-29; page 19, lines 18-19) in the art-preferred model (LDLR deficient mice) for studying the biochemical and morphologic effects of atherosclerosis and that one of ordinary skill in the art, using the teachings of the instant invention, would be able to readily determine the corresponding doses useful in humans, without undue experimentation.

8. We prepared and orally administered various dosages of isolated copper-oxidized LDL to mice according to the teachings of the instant specification and evaluated the aortic sinus lesion area in the aorta. As shown in Figure 1 appended hereto, oral administration of isolated copper-oxidized LDL decreases the aortic sinus lesion area by 45% as compared to non treated mice at several tested dosages per mouse (10μg, 100μg or 1000μg). Further, as shown in Figure 2 appended hereto, when mice were orally administered isolated copper-oxidized LDL at varying mg/kg body weight dosages (0.35mg/kg, 3.5mg/kg or 35mg/kg) results showed decreases in the aortic sinus lesion area similar to results shown in Figure 1. These results show that a skilled artisan can, as a matter of routine, readily determine the appropriate therapeutically effective dose in humans.

9. I also understand that claims 14, 19, 27 and 28 are rejected under 35 U.S.C. §103(a) as being unpatentable over Sima et al., *11th Int. Symp on Atherosclerosis*, page 227, October 1997 ("Sima") and Hansson et al., *11th Symp on Atherosclerosis*, page 289, October 1997 ("Hansson") in view of U.S. Patent No. 6,541,011 to Punnonen ("Punnonen").

10. As described at the interview, neither of Sima and Hansson suggest any desirability or incentive to orally administer an enteric coated composition comprising isolated copper-oxidized LDL to treat atherosclerosis. In contrast, those preferences clearly teach that OxLDL contributes to the development of atherosclerosis (*i.e.*, OxLDL is pro-atherosclerotic) -- teaching away from the claimed invention. Additionally, OxLDL is ingested on a daily basis as part of a routine diet and OxLDL is degraded in the gut following ingestion. For this reason, at the time the application was filed, one of ordinary skill in the art would not be motivated to combine Sima and Hansson with Punnonen with a reasonable expectation of success. The results described in the specification demonstrate that the composition of the claimed invention (enteric coated composition comprising isolated copper-oxidized LDL and a pharmaceutically acceptable carrier for oral administration) displays the unexpected ability to treat atherosclerosis.

11. I further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that willful false statements may jeopardize the validity of this application and any patent issuing therefrom.

Dror Harats

Signed this 4 day of December, 2005

Encl:
Appendix I